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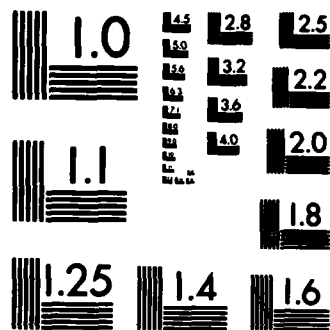
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ANNUAL REPORT

Larry G. McCoy and Craig R. Hassler

July 15, 1978

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DADA17-69-C-9118

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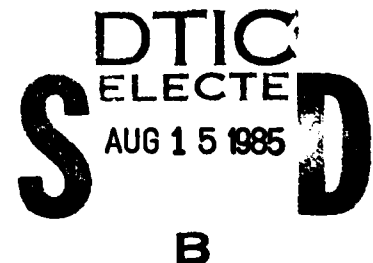
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Material processing studies were conducted to develop porous tricalcium phosphate materials of different stoichiometry. These two portions of the study were to further understanding of the basic question: Is the optimal material for bone ingrowth and biodegradation going to be produced by alterations in stoichiometry or alterations in pore structure within the material of the given stoichiometry?

Previously, numerous tricalcium phosphate powders were produced having controlled calcium to phosphate ratios. Specifically, three powders were prepared using the standard technique of modifying composition of tribasic calcium phosphate powders by the addition of phosphoric acid. After three powders of various composition were made at Battelle, the powders were mill-blended and submitted for verification analysis. Materials were then fired and analyzed by X-ray defraction to determine the crystalline phases that might be present in the finished implants. The results of the study indicated that preparation of a single phase variable composition material does not appear possible using standard methods even though beta phase tricalcium phosphate will be the predominant phase in all materials, secondary phases of monetite or hydroxyapatite were always found depending upon what border of the compositional range the compound fell. Consequently, these three different materials were not developed further. Instead, material of various pore structure confirmation was developed for in vivo implant studies.

✓ Three different materials of various pore structures were designed and fabricated into rectangular segments for implanting in the previously used rabbit calvarium model. Animals implanted will be observed for periods of 3, 6, 9, and 12 months, respectively. Each time period, a portion of the animal population will be necropsied. Analysis by histology and radiography will be performed.

ABSTRACT

This report summarizes results of continued studies for further developing and understanding the in vivo behavior of resorbable calcium phosphate for use in the management of hard tissue avulsive wounds and orofacial fractures.

Specific studies have been devoted to the preparation and comparative in vivo evaluation of porous tricalcium phosphates having various pore distributions. Materials for in vivo studies were prepared and animal studies were initiated.

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SUMMARY

Research studies were continued to further our understanding of the in vivo behavior of resorbable calcium phosphate ceramics for use in the management of hard tissue avulsive wounds and orofacial fractures.

Material processing studies were conducted to develop porous tricalcium phosphate materials of different stoichiometry. These two portions of the study were to further understanding of the basic question: Is the optimal material for bone ingrowth and biodegradation going to be produced by alterations in stoichiometry or alterations in pore structure within the material of the given stoichiometry?

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FOREWORD

This study has been conducted at Battelle's Columbus Laboratories utilizing the talents and resources of the Ceramic Materials Section and the Bioengineering/Health Sciences Section. This is the Sixth Annual Progress Report under Contract No. DADA17-69-C-9118, "Management of Hard Tissue Avulsive Wounds and Management of Orofacial Fractures". The Principal Investigator for this research was Mr. Larry G. McCoy. The physiologist for the animal implant studies was Dr. Craig Hassler.

We would like to acknowledge the valuable assistance of Mr. Roger K. Beal for his excellent work in preparation of the porous implant materials.

In conducting the research described in this report, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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BACKGROUND, PROBLEM AND APPROACH

Historically, various techniques have been employed for the repair or treatment of osseous diseases, defects, and wounds. Autogeneous bone grafting remains the most satisfactory approach but is not without the disadvantages associated with double surgeries and the limitations imposed on the repair of massive osseous defects.

Since April, 1970, Battelle's Columbus Laboratories has been conducting research under contract with the Dental Research Division, U.S. Army Medical Research and Development Command, on the development of resorbable ceramics for potential application in the repair of hard tissue avulsive wounds. The basic materials have been calcium phosphates. These materials were selected because they contain two of the essential elements of the natural bone mineral phase, calcium hydroxyapatite.

In vivo studies were conducted initially at U.S. Army Institute of Dental Research (USAIDR), using the sintered porous materials and slurries prepared at Battelle from tricalcium phosphate $\text{Ca}_3(\text{PO}_4)_2$ and other calcium orthophosphate powders CaHPO_4 and $\text{Ca}(\text{H}_2\text{PO}_4)_2$, to evaluate the potential use of calcium phosphates to both facilitate repair of bone defects and to determine the best material for future exploration(1-3). The implant studies indicated that calcium phosphates consisting essentially of the mineral phases $\text{Ca}(\text{PO}_3)_2$, $\text{Ca}_3(\text{PO}_4)_2$, and CaHPO_4 are well tolerated by the tissue, appear to be nontoxic, are resorbable, and permit rapid invasion of new bone.

Of the various porous calcium phosphate materials investigated, tricalcium phosphate, $\text{Ca}_3(\text{PO}_4)_2$, was selected for continued development and evaluation since it was easy to fabricate and was found to be both biocompatible and resorbable. Emphasis has been directed toward producing low-density porous materials consisting of single-phase tricalcium phosphate(4-7).

Although previous implant studies at USAIDR have demonstrated that porous tricalcium phosphate is biocompatible, resorbable, and promotes or permits rapid ingrowth of new bone, histological evidence indicated persistence of a residual ceramic structure as long as 1 year after implantation. This structure appeared to be composed of an isomorphic distribution of small encapsulated ceramic particles. The presence of this residue would be

expected to retard complete remodeling of the bone and the attendant strength development.

As a result of this problem, the primary emphasis of continued studies was directed toward the development of porous materials having improved (increased) resorption rates. This objective may be achieved either by changes in structure or chemistry of the ceramic implant material.

To provide basic resorption rate data on the in vivo behavior of the tricalcium phosphate bioresorbable ceramics, implant studies were initiated in 1975 at BCL using the rabbit calvarium model(8). Historic samples of tricalcium phosphate were implanted as a control and samples of two new materials were implanted for comparative observation. These new materials were prepared using the improved processing techniques derived in previous materials development studies and represented significant improvements in the structural characteristics of porous tricalcium phosphate. The characterization of the materials involved and the results of the in vivo studies were the subject of the Fifth Annual Report(8).

These results indicated that the improved material exhibited significant increases in resorption rate. In fact, the material resorbed so rapidly that after the ninth month the implant appeared to be granulated and was invaded with connective tissue. This result does not imply lack of biocompatibility but does suggest that such rapid degradation can be deleterious in stress-bearing situations. It is not known whether the enhanced resorptivity resulted from achieving a Ca/P ratio closer to the theoretical for tricalcium phosphate or from the improvements in the structural characteristics of the material.

To discern the effects of structural variations on resorption rate, experimental porous implants were prepared using a single tricalcium phosphate powder but having different pore size distribution. Three materials were prepared for in vivo evaluation.

MATERIALS AND METHODS

Porous Materials Development

Material processing and fabrication studies were continued to develop experimental porous tricalcium phosphate implant materials for in vivo evaluation of the effects of structural variations on resorption rate. The effort has involved the preparation of porous implants of a fixed composition in which the pore size distributions were systematically varied to determine if pore size distributions could be selectively modified to control resorption rate. Three materials were prepared for in vivo evaluation. The characteristics of these materials are summarized in Table 1.

The fabrication of the Group 1 and 2 materials was completed in the previous program year, the details of which are discussed in the Fifth Annual Report dated June 1976. It was the original intent in the preparation of the Group 3 material to induce a microporosity in the 35-45 micron range and thereby enhance the resorption rate by increasing the permeability and internal surface area of the material. However, histologic evidence from previous implant studies became available during later stages of the material fabrication studies, which indicated that materials having the improved Group 1 type structure had such significantly increased resorption rates that further increases would be hazardous to the mechanical stability of the implant. As a consequence, a new Group 3 material was prepared having a coarser pore structure than the Group 1 material. The intent was to induce rapid bone ingrowth into the larger pores while reducing the resorption by having thicker wall sections between the pores.

The new Group 3 material was prepared by using the coarsest (-40/+60 mesh) fraction of the standard (technical grade) naphthalene distribution. The standard technique of intensive roll blending was used to achieve stable phosphate powder/naphthalene blends. Three blocks of material for sectioning into implants were prepared by the standard hydropressing and sintering procedures used for the Groups 1 and 2 materials. Three implants were cut from the two blocks having the most identical structures (Blocks E39 and E41) and were dry heat sterilized at 600°F for 4 hours.

TABLE 1. MODIFIED PORE STRUCTURE EXPERIMENTAL IMPLANT MATERIALS

Batch(a) Number	Designation	Naphthalene(b) Pore Size Distribution	Calculated(c) Mean Pore Size (microns)	Sintered Density
E22	Standard	Group 1	260	48.6
E26	Modified-Fine	Group 2	210	47.0
E39	Modified-Coarse	Group 3	290	49.7

(a) All specimens were prepared using Batch D-22 tricalcium phosphate powder and technical grade naphthalene. All specimens were sintered at 2050°F for 4 hours.

(b) Napthalene particle size distributions (weight percent):

	-40/+60	Mesh Size -60/+80	-80/+100
	Average Particle Size (microns)		
	335	213	163
Group 1	76	18	6
Group 2	40	20	40
Group 3	100	--	--

(c) Assuming spherical shape and 15 percent linear shrinkage during sintering.

EXPERIMENTAL ANIMAL STUDIES

This portion of the report details the various research procedures which are used in our laboratories to evaluate biodegradable materials. The evaluative procedures include histology, radiography, and blood and urine chemistries. The classical techniques of histology and radiography are the key diagnostic procedures.

In order to test the biodegradation of large tricalcium phosphate segments, a special experimental model has been devised in this laboratory. We utilize the calvarium of a mature, male New Zealand White rabbit with a minimum weight of 8 pounds. The calvarium has been found to be an excellent implant site for this relatively weak structural biomaterial since stresses upon the calvarium are not extraordinarily high and external stabilization is not required. Consequently, confusing effects which might be due to fixation devices are not seen. Of greater importance is the fact that this implant site provides the researcher with a large, relatively uniform area of material for various simultaneous studies. Additionally, periodic radiography of this flat area is an easy matter.

Standard aseptic surgical technique was used to expose the calvarium of the animal. A rectangular (0.25 inch x 0.75 inch) portion of the calvarium was osteotomized from the animal with no attempt to salvage the periosteum overlying the removed area. To match the curvature of the rabbit calvarium, specifically shaped samples of tricalcium phosphate were fabricated with a thickness of 0.1 inch.

Three different experimental groups of three animals each were followed. These groups were implanted with chemically identical tricalcium phosphate implants which differed in pore size distribution and orientation of porosity. Four research animals were included in each group. One animal from each group will be sacrificed at intervals of 3, 6, 9, and 12 months.

Blood and 24-hour urine samples were taken pre-implant, and will be taken at 3-month intervals, and at the time of necropsy for all animals and the calcium and phosphorous levels determined. The animals will be radiographed at 3-month intervals until the time of necropsy and the excised skulls will be radiographed post-necropsy.

RESULTS AND CONCLUSIONS

Materials of varying pore structures were successfully prepared and these materials were implanted into the calvaria of New Zealand White rabbits. At the time of this report, no in vivo results were available. Consequently the success or failure of these studies will not be available until the next annual report.

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